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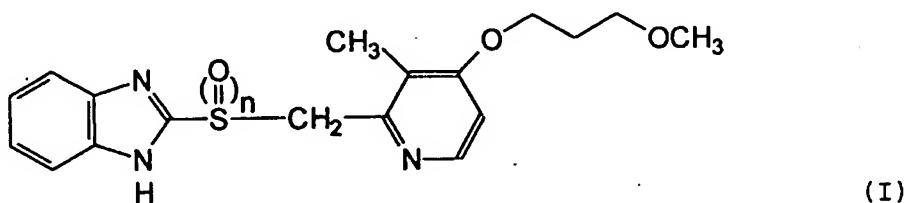
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(54) Benzimidazole derivatives as antimicrobial agent against *Campylobacter pylori*.

(57) The compounds having the following formula (I)



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wherein n is 0 or 1; or the pharmaceutically acceptable salts thereof may be used for the preparation of a medicament for preventing, improving and treating a disease caused by the bacterium *Campylobacter pylori*, in particular peptic ulcer or gastritis or infectious diseases, and for eradicating the bacterium *Campylobacter pylori* from the mucous membrane of a patient and preventing recurrence of a disease caused by *Campylobacter pylori*.

The invention relates to an antimicrobial agent, an antibiotic, anti-bacterial medicine which prevents, improves and therapeutically treats a disease caused by *Campylobacter pylori*, called hereinafter *C. pylori*. This organism is a microaerophilic, gram-negative spirillar rod and it is thought to cause infectious diseases such as diarrhea and food poisoning. Some investigators have also proposed that *Campylobacter pylori* 5 may participate in the pathogenesis of gastritis and in particular the recurrent form thereof. In 1989, it was proposed to rename *C. pylori* to *Helicobacter pylori* based on further research in the fields of bacteriology and bacterial taxonomy. Therefore, *C. pylori* is also called *H. pylori*.

## Statement of prior art

10 In the state of the art, many substances have been used for prevention, treatment or cure of stomach and duodenum diseases such as gastritis or peptic ulcers, gastric ulcers and duodenal ulcers. Especially, histamine H<sub>2</sub>-receptor antagonists such as cimetidine or ranitidine have been widely used. Histamine H<sub>2</sub>-receptor antagonists quickly improve a damaged stomach and duodenal mucous membrane, and they 15 reduce subjective symptoms such as stomach pain immediately. However, the problem remains that these diseases will recur very often after they have been healed and the medication has been ceased.

It is reported in the Medical Journal of Australia, volume 142, pages 436-439, 1985 and American Journal of Gastroenterology, volume 82, pages 192-199, 1987 that healthy volunteers to whom *C. pylori* was administered orally, started to show symptoms of acute gastritis. Gastroenterology, volume 94, pages 33-20 40, 1988 reported that the injured gastric tissue was found to improve when *C. pylori* was eradicated by administration of antibiotic substances. Thus, it was shown that some forms of gastritis are actually caused by *C. pylori* and can be effectively treated by eliminating *C. pylori*.

In the state of the art, medicines which can eradicate *C. pylori* include antibiotics such as ampicillin, 25 cefalexin, ofloxacin, minocycline and roxithromycin and medicaments for gastritis such as plaunotol, sofalcone, benexate hydrochloride and colloidal bismuth subcitrate. Among these substances which can clear *C. pylori*, prior medicines for gastritis provide an eradication activity which is too weak in a usual dosage of administration. The antibiotics mentioned above have a good efficacy against *C. pylori*, but some side-effects such as allergy or diarrhea will often occur, and then, after long term administration, they sometimes cause severe irreversible adverse reactions such as hematological disorders or gastrointestinal 30 disorders. And growth of resistant bacteria easily occurs. From a clinical point of view, a good medicine is desired for reliable prevention and therapy and for a long term medication of gastritis, in particular the recurrent form of gastritis, with safety. There is continuing research for a medicine which can eradicate *C. pylori* in a usual dosage of administration with safety in the long term medication.

JP-A 2-209809, corresponding to US 5 093 342 discloses that 5-Methoxy-2-[(4-methyl-3,5-dimethyl-2-pyridinyl)-methylsulfinyl]-1H-benzimidazole, called omeprazole, or a salt thereof, being an acid secretion-inhibiting medicine for gastritis etc., has antibiotic activity against *C. pylori* 8005, which is one particular clinical isolate of *Campylobacter pylori*. On the other hand, Scand. J. Gastroenterol., 24 (1989), 12-15, and Scand. J. Gastroenterol. 24 (suppl. 167), (1989), 49-54, disclose tests to demonstrate that omeprazole shows no antimicrobial activity on *Campylobacter pylori* in vivo.

40 JP-A 3-173817, corresponding to US 5 013 743 discloses the compounds (1) to (14) shown below exhibiting an antibiotic activity against the standard strains *C. pylori* NCTC-11916 and NCTC-11637, and the clinical isolates *C. pylori* PCL-56, CPY-0011-1, KS-13, CLO-1 and CLO-6.

- (1) 2-[{3-Methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl}-methylsulfinyl]-1H-benzimidazole
- (2) 2-(3,5-Dimethyl-4-methoxypyrid-2-yl)methylsulfinyl-5-methoxy-1H-benzimidazole
- (3) 2-[{3-Methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyrid-2-yl}-methylsulfinyl]-1H-benzimidazole
- (4) 2-[{3-Methyl-4-(2,2,3,3-tetrafluoropropoxy)pyrid-2-yl}-methylsulfinyl]-1H-benzimidazole
- (5) 2-[{3-Methyl-4-(2,2,3,3,4,4-hexafluorobutoxy)pyrid-2-yl}-methylsulfinyl]-1H-benzimidazole
- (6) 2-[{3-Methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl}-methylthio]-1H-benzimidazole
- (7) 2-[{(4-Isobutoxy)pyrid-2-yl}methylthio]-1H-benzimidazole
- (8) 2-[{(4-Isobutoxy)pyrid-2-yl}methylthio]-5-trifluoromethyl-1H-benzimidazole
- (9) 2-[{(4-Isoproxy)pyrid-2-yl}methylthio]-5-trifluoromethyl-1H-benzimidazole
- (10) 2-[{(4-2'-Propenyl)oxy}pyrid-2-yl]methylthio]-5-trifluoromethyl-1H-benzimidazole
- (11) 2-[{(4-Propargyl)oxypyrid-2-yl}methylthio]-5-trifluoromethyl-1H-benzimidazole
- (12) 2-[{3-Methyl-4-(2,2,3,3-tetrafluoropropoxy)pyrid-2-yl}methylthio]-1H-benzimidazole
- (13) 2-[{3-Methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyrid-2-yl}methylthio]-1H-benzimidazole
- (14) 2-[{3-Methyl-4-(2,2,3,3,4,4-hexafluorobutoxy)pyrid-2-yl}methylthio]-1H-benzimidazole

JP-A 3-48680 discloses the below shown compounds being antibiotic against *C. pylori*, failing to show tested strains.

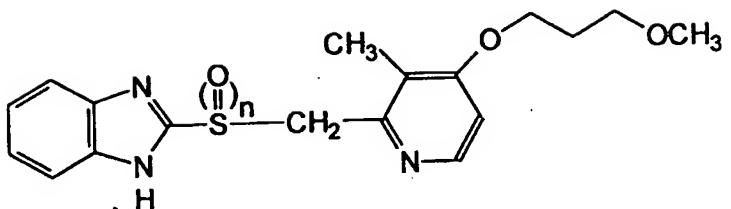
- (1) 2-[3-Methyl-4-(1-methyl-2-piperidyl)methoxy-2-pyridyl]-methylthio-1H-benzimidazole
- (2) 2-[3-Methyl-4-(3-morpholinopropoxy)-2-pyridyl]methylthio-1H-benzimidazole
- (3) 2-[3-Methyl-4-(2-piperidinoethoxy)-2-pyridyl]methylthio-1H-benzimidazole
- (4) 2-[3-Methyl-4-(2-(2-oxo-1-pyrrolidinyl)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole
- 5 (5) 2-[3-Methyl-4-(2-morpholinoethoxy)-2-pyridyl]methylthio-1H-benzimidazole
- (6) 2-[3-Methyl-4-(3-piperidinopropoxy)-2-pyridyl]methylthio-1H-benzimidazole
- (7) 5-Methoxy-2-[3-methyl-4-(2-morpholinoethoxy)-2-pyridyl]methylthio-1H-benzimidazole
- (8) 5-Methoxy-2-[3-methyl-4-{2-(N-benzyl-N-methylamino)-ethoxy}-2-pyridyl]methylthio-1H-ben-  
zimidazole
- 10 (9) 2-[3-Methyl-4-[2-{N-methyl-N-(2-phenylethyl)amino}-ethoxy]-2-pyridyl]methylthio-1H-benzimidazole
- (10) 2-[3-Methyl-4-[2-(N-methyl-N-(3-phenylpropyl)amino)-ethoxy]-2-pyridyl]methylthio-1H-benzimidazole
- (11) 2-[3-Methyl-4-{2-(N-benzyl-N-ethylamino)ethoxy}-2-pyridyl]methylthio-1H-benzimidazole
- (12) 2-[3-Methyl-4-{2-(N-benzyl-N-propylamino)ethoxy}-2-pyridyl]methylthio-1H-benzimidazole
- 15 (13) 2-[3-Methyl-4-[2-{N-methyl-N-(4-methylbenzyl)amino}-ethoxy]-2-pyridyl]methylthio-1H-ben-  
zimidazole
- (14) 2-[3-Methyl-4-[2-{N-(4-chlorobenzyl)-N-methylamino}-ethoxy]-2-pyridyl]methylthio-1H-benzimidazole
- (15) 2-[3-Methyl-4-[2-{N-(4-bromobenzyl)-N-methylamino}-ethoxy]-2-pyridyl]methylthio-1H-benzimidazole
- (16) 2-[3-Methyl-4-{2-(1,2,3,4-tetrahydroisoquinoline-2-yl)ethoxy}-2-pyridyl]methylthio-1H-benzimidazole
- (17) 1/2 magnesium salt of 2-[3-methyl-4-{2-(N-benzyl-N-methylamino)ethoxy}-2-pyridyl]methylsulfinyl-  
20 1H-benzimidazole
- (18) 1/2 magnesium salt of 2-[3-Methyl-4-[2-{N-methyl-N-(4-methylbenzyl)amino}ethoxy]-2-pyridyl]-  
methylsulfinyl-1H-benzimidazole
- (19) 1/2 magnesium salt of 2-[3-Methyl-4-[2-{N-(4-bromobenzyl)-N-methylamino}ethoxy]-2-pyridyl]-  
methylsulfinyl-1H-benzimidazole
- 25 (20) 2-[3-Methyl-4-[2-(1,2,3,4-tetrahydroisoquinoline-2-yl)ethoxy]-2-pyridyl]methylsulfinyl-1H-ben-  
zimidazole
- (21) 2-[3-Methyl-4-[2-(N-benzyl-N-methylamino)ethoxy]-2-pyridyl]methylsulfonyl-1H-benzimidazole
- (22) 2-[3-Methyl-4-[2-(N-methyl-N-(4-methylbenzyl)amino)-ethoxy]-2-pyridyl]methylsulfonyl-1H-ben-  
zimidazole
- 30 In the medication of diseases caused by C. pylori, it is necessary to have an excellent activity against a broad spectrum of C. pylori including standard strains and clinical isolates. The antibiotics effective against C. pylori have a minimum inhibitory concentration called MIC ( $\mu\text{g}/\text{ml}$ ) in the range of about 1  $\mu\text{g}/\text{ml}$  or less. Therefore, whether a compound has a MIC in that range or not is a criterion to evaluate its clinical efficacy against C. pylori.
- 35 Under the above shown point of view, omeprazole disclosed in JP-A 2-209809 and JP-A 3-173817 has no sufficient antibiotic activity. Among the other 14 compounds shown in JP-A 3-173817, the compounds (12), (13) and (14) are the only antibiotics in respect of activity against all the tested strains. JP-A 3-48680 shows that the compounds have an MIC of 1 microgram per ml or less to only one tested strain. It is not expected from the listed data that they will have a wide antibiotic activity against many strains.
- 40 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylsulfinyl]-1H-benzimidazole (I;  $n=1$ ) and 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylthio]-1H-benzimidazole (I;  $n=0$ ) are known from JP-A 1-6270, corresponding to EP-A 268 956, as acid secretion inhibitors having an anti-ulcer activity. They can be prepared according to Examples 32 and 31, respectively, disclosed in JP-A-1-6270. However, the antimicrobial activity of these compounds is not referred to.

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#### Disclosure of the Invention

The inventors made investigations with 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylsulfinyl]-1H-benzimidazole (I;  $n=1$ ) and 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylthio]-1H-benzimidazole (I;  $n=0$ ) and surprisingly found them to have the same C. pylori-eradicating activity as an antibiotic substance. This is how the inventors have reached the invention. The two compounds of the invention have the following chemical structure:

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(I)

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wherein n is 0 or 1, respectively.

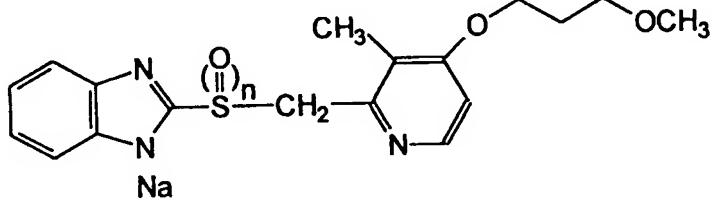
The invention provides the use of a pharmacologically effective amount of a compound having the above formula (I) wherein n is 0 or 1, or a pharmacologically acceptable salt thereof for the preparation of a medicament for preventing, improving or treating a disease caused by *Campylobacter pylori* in a mammal suffering from such a disease. It is preferable that the mammal is a human being and the disease is peptic ulcer or gastritis, in particular the recurrent form thereof. The disease may also be an infectious disease caused by *Campylobacter pylori* such as diarrhea and food poisoning.

Moreover, the invention provides the use of a compound having the above formula (I) wherein n is 0 or 1, or a pharmacologically acceptable salt thereof for the preparation of a medicament for eradicating *C. pylori* from the mucous membrane of the stomach of a patient suffering from a gastric ulcer, duodenal ulcer or gastritis if the medicament is administered in a pharmacologically effective amount to the patient; the use of a pharmacologically effective amount of a compound having the above formula (I) wherein n is 0 or 1, or a pharmacologically acceptable salt thereof for the preparation of a medicament for preventing recurrence of a disease caused by *C. pylori* in a mammal suffering from said disease; and the use of a pharmacologically effective amount of a compound having the above formula (I) wherein n is 0 or 1 or a pharmacologically acceptable salt thereof for the preparation of a medicament for restraining the adverse activity of *C. pylori* to cause a peptic disease in a mammal.

The invention further provides an antimicrobial medicine or agent comprising a compound having the formula (I) wherein n is 0 or 1, or a pharmaceutically acceptable salt thereof to prevent, improve or treat an ulcer and/or gastritis. In the invention, the pharmacologically acceptable salt of the compound (I) wherein n is 0 or 1, includes an addition salt thereof with an inorganic acid such as hydrochloric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, nitric acid, perchloric acid and phosphoric acid, an addition salt thereof with an organic acid such as citric acid, maleic acid, fumaric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid, and a salt thereof with a metal such as sodium, potassium, calcium and magnesium. The sodium salts, in particular those having the following formula (II) are most preferable for administration:

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(II)

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wherein n is 0 or 1.

The invention provides a medicine which is effective for the *C. pylori* eradication having the same effect as antibiotics. The compounds of the invention can be administered for a long time with safety and without side effects. They are pharmacologically effective and clinically useful against diseases caused by *Campylobacter pylori*, in particular peptic ulcer or (recurring) gastritis.

The compounds of the invention have the following physical properties:

Physical properties of 2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]-methylsulfanyl]-1H-benzimidazole (I; n=1):

molecular formula : C<sub>18</sub>H<sub>20</sub>N<sub>3</sub>O<sub>3</sub>S  
molecular weight : 358.44  
appearance : white crystalline  
Physical properties of 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylthio]-1H-benzimidazole (I;  
5 n = 0):  
molecular formula : C<sub>18</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub>S  
molecular weight : 342.44  
appearance: pale yellow crystalline

10 Pharmacological Test 1:

Standard strains and clinical isolates of *C. pylori* derived from the mucous membrane of the stomach were used and determined in vitro according to the agar dilution method by Nihon Kagaku Ryoho Gakkai (English name: Japan Society of Chemotherapy).

15 The sodium salt of 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylsulfinyl]-1H-benzimidazole (I; n = 1) was dissolved in sterilized water. 2-[(4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)-methylthio]-1H-benzimidazole (I; n = 0) and, as controls, omeprazole, 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole and 2-[(3-Methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl)methylthio]-1H-benzimidazole were dissolved separately in a 1% dimethylsulfoxide solution. As antibiotic control substances,  
20 roxithromycin as a macrolide, ampicillin as a penicilline and ofloxacin as a quinolone were dissolved in a buffer solution of acetic acid having a pH of 5.0, sterilized water and an 1N aqueous solution of NaOH, respectively. Test plates were prepared by adding 7% horse blood to Brucella agar named by BBL Microbiology Systems (tradename), being available from Bector Dickson and Company. The incubation was conducted at 37 °C at a pH of 7.0 for 3 days under microaerophilic conditions using Canipack (tradename)  
25 being available from Bector Dickson and Company. MIC was determined in units of microgram per ml. Test results are shown in Table 1. NCTC11637 and NCTC11916 are standard strains. The other references indicate clinical isolates.

The test result is shown in terms of the antibiotic activity (MIC) in units of microgram/ml, obtained in vitro against *C. pylori*. The tested compounds are:

30 (1) sodium salt of 2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]methylsulfinyl-1H-benzimidazole,  
(2) 2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]methylthio-1H-benzimidazole,  
(3) 5-Methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridine-2-yl)methylsulfinyl-1H-benzimidazole (omeprazole),  
(4) 5-Methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinyl)methylthio-1H-benzimidazole,  
(5) 2-[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridine-2-yl)methylthio-1H-benzimidazole,  
35 (6) roxithromycin (RXM),  
(7) ampicillin (ABPC),  
(8) ofloxacin (OFLX).

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Table 1

Tested strain	Compound							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
NCTC11637	3.13	0.8	50	25	25	0.4	0.1	0.8
NCTC11916	3.13	0.2	25	12.5	12.5	0.1	0.05	0.8
EI-2	3.13	0.4	25	25	25	0.2	0.4	0.8
EI-5	3.13	0.2	50	25	12.5	0.2	0.4	0.8
EI-36	6.25	0.4	25	12.5	12.5	0.2	0.2	0.8
EI-46	3.13	0.4	25	12.5	12.5	>100	0.05	3.13
EI-391	3.13	1.56	50	25	12.5	50	0.1	25
EI-393	3.13	1.56	50	25	25	0.2	0.1	0.8
EI-397	3.13	1.56	50	25	25	0.2	0.1	0.8
EI-429	1.56	1.56	25	25	25	0.2	0.2	0.8
EI-467	1.56	1.56	50	12.5	12.5	0.2	0.05	0.4
EI-612	0.4	0.8	25	12.5	6.25	0.2	0.05	0.8
EI-925	3.13	0.4	25	12.5	12.5	0.2	0.2	0.4
EI-930	3.13	0.4	25	12.5	12.5	0.4	0.4	0.8
EI-933	3.13	0.8	25	12.5	12.5	0.1	0.05	0.4

It is noted from the test results that the compounds of the invention are superior to known compounds such as omeprazole derivatives disclosed in JP-A 2-209809 and lansoprazole derivatives (6) disclosed in JP-A 3-173817. The compounds of the invention evidently provide an equivalent C. pylori eradicating activity to antibiotics.

#### Pharmacological Test 2:

The following compounds (1) to (11) were tested in the same way as shown in Pharmacological Test 1 and the results are shown in Table 2.

- (1) sodium salt of 2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]methylsulfinyl-1H-benzimidazole,
- (2) 2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl)methylthio-1H-benzimidazole,
- (3) 5-Methoxy-2-(4-methoxy-3,5-dimethylpyridine-2-yl)methylsulfinyl-1H-benzimidazole (omeprazole),
- (4) 5-Methoxy-2-(4-methoxy-3,5-dimethylpyridine-2-yl)methylthio-1H-benzimidazole (thioether of omeprazole),
- (5) 2-[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridine-2-yl]methylthio-1H-benzimidazole (thioether of lansoprazole),
- (6) roxithromycin (RXM),
- (7) ampicillin (ABPC),
- (8) ofloxacin (OFLX),
- (9) 2-[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridine-2-yl]methylsulfinyl-1H-benzimidazole (lansoprazole),
- (10) 2-[3-Methyl-4-(2-morpholinoethoxy)pyridine-2-yl]methylthio-1H-benzimidazole (disclosed in JP-A 3-48680),
- (11) 2-[3-Methyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-2-yl]methylsulfinyl-1H-benzimidazole (disclosed in US-A 5 013 743)

Table 2

Tested strain	Compound								(11)	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)		
NCTC11637	0.8	0.8	50	12.5	1.56	0.2	0.1	0.8	6.25	1.56
NCTC11916	1.56	1.56	50	12.5	1.56	0.1	0.1	0.8	12.5	1.56
CLO 2	0.8	0.8	25	12.5	1.56	0.2	0.4	1.56	6.25	1.56
CLO 4	1.56	0.8	50	12.5	3.13	0.8	0.8	1.56	6.25	3.13
CLO 5	1.56	0.8	25	12.5	1.56	0.2	0.05	0.8	6.25	1.56
CLO 6	>100	>100	>100	>100	0.8	0.4	0.4	>100	>100	>100
CLO 36	0.4	0.4	25	6.25	0.8	0.2	0.1	0.8	3.13	1.56
CLO 46	0.8	0.8	25	12.5	1.56	>100	0.1	1.56	6.25	0.8
BI-391	0.8	0.8	25	12.5	1.56	>100	0.2	25	6.25	1.56
BI-393	0.8	0.8	25	12.5	1.56	0.2	0.4	0.8	6.25	1.56
BI-397	0.8	0.8	25	12.5	1.56	0.2	0.4	0.8	6.25	1.56
BI-429	0.8	0.8	25	12.5	1.56	0.2	0.2	0.8	6.25	1.56
BI-467	1.56	0.8	25	12.5	1.56	0.4	0.1	0.8	6.25	3.13
BI-612	0.4	0.4	25	6.25	0.8	0.2	0.05	0.8	3.13	1.56
BI-930	0.8	0.8	50	12.5	1.56	0.2	0.8	1.56	6.25	1.56
BI-933	1.56	0.8	50	12.5	1.56	0.4	0.4	0.8	6.25	1.56
BI-934	>100	>100	>100	>100	0.1	0.4	0.4	>100	>100	>100
H 12	1.56	0.8	25	12.5	1.56	0.4	0.1	0.8	6.25	1.56
H 13	0.8	0.8	25	12.5	1.56	0.1	0.1	0.8	3.13	1.56
H 16	1.56	1.56	50	12.5	1.56	0.2	0.1	0.8	6.25	1.56
H 21	0.8	0.8	25	12.5	1.56	0.2	0.2	0.8	3.13	1.56
H 26	1.56	0.8	50	12.5	1.56	0.4	0.05	0.8	6.25	1.56
H 30	0.8	0.8	25	12.5	1.56	0.2	0.2	0.8	6.25	1.56

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It is noted from the data of Table 1 and Table 2 that the compounds of formula (I) according to the invention wherein n is 0 or 1, are superior to omeprazole, 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridine-2-yl]-methylthio-1H-benzimidazole and 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-3-pyrido-2-yl]-methylsulfinyl-1H-benzimidazole and at the same time they have almost the same C. pylori-eradicating activity as antibiotic substances.

Since the compounds of the invention are not antibiotic substances in the usual sense, they are effective against resistant bacteria such as El-46 and El-391 of the clinical isolated strains shown in Table 1. This is the reason why they provide an eradicating activity to a wider variety of bacteria than conventional antibiotic substances. They can be administered to a mammal and the human being for a long time. They 5 selectively eradicate C. pylori, not inhibiting the growth of other gram positive bacteria and gram negative bacteria even at a concentration being as high as 100 µg per ml or above. This shows the fact that they can selectively be antibiotic against C. pylori.

#### Acute Toxicological Test:

10 The compound (I; n=1) of the invention was administered intravenously or orally one time, with a carrier of saline, to Slc:SD rats and Slc:ICR mice, each being 7 or 8 weeks old, in a group consisting of five males and five females, to determine LD<sub>50</sub> values. Results are shown in Table 3.

The acute toxicity of the compound (I; n=1) is shown in terms of LD<sub>50</sub> in units of mg/kg.

15

Table 3

administration route	rats		mice	
	male	female	male	female
intravenous	157 mg/kg	152 mg/kg	220 mg/kg	237 mg/kg
oral	1447 mg/kg	1332 mg/kg	1206 mg/kg	1012 mg/kg

25 The obtained LD<sub>50</sub> values are 5000 times as much as a clinical dosage of oral administration and for this reason the compounds of the invention are found to be greatly safe, that is, providing no toxicological influence.

#### Technological Advances of the Invention:

30 It is evident from the above test data that the compounds of the invention are as antibiotically active against C. pylori as conventional antibiotic substances and therefore can work pharmacologically to prevent, improve and therapeutically treat diseases caused by C. pylori such as peptic ulcer or gastritis and some infectious diseases. They can prevent, improve and therapeutically treat these diseases, particularly 35 recurring gastritis caused by C. pylori, with safety. They can be administered continuously for a long term, without combination of another antibiotic substance. The compounds can be used as an antibiotic medicine.

#### Application of the Invention:

40 The compounds of the invention can be administered, without any limitation, in normal ways. Which way and what amount is to be used for medication depends on the condition of the patient, the kind of ulcer and/or gastritis, the degree or extent of the disease, age of the patient and functions of heart, liver and kidney. It is preferable in the invention that the compounds of the invention are dosed orally in an amount of 45 0.01 to 100 mg per day, more preferably 0.1 to 80 mg, further preferably 0.1 to 60 mg, most preferably 5 to 40 mg. The oral medication can be conducted in the form of powder, granule, tablet or capsule. They can be prepared with a normally used carrier according to prior art methods, preferably according to the methods shown in JP-A 1-290628 and JP-A 2-22225, corresponding to US 5 035 899. The preparation may further include therein a forming filler, a binder, a disintegrating agent, a lubricant, a colorant, a corrigent, a taste-improver and/or a smell-improver.

50 The filler includes lactose, corn starch, white sucrose, glucose, mannitol, sorbitol, crystalline cellulose and silicon dioxide ; the binder includes polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone ; the disintegrating agent includes starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, carboxymethyl cellulose, calcium and pectin; the lubricant includes magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils ; the colorant may be any one which is permitted for drugs ; the corrigent includes cacao powder, mentha herb, aromatic powder, mentha oil, borneol and powdered cinnamon bark. Of course, these tablets and granules 55 may be, if necessary, coated with sugar, gelatin or the like.

Examples of preparations of the medicines of the invention, including orally dosed preparations and those with a enteric coating including the compound (I) wherein n is 0 or 1, of the invention are shown below. These do not mean any limitation to the invention.

5 Example 1

Tablets including the compound (I; n = 1): 2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]-methylsulfinyl-1H-benzimidazole were prepared by the below shown prescription.

2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]-methylsulfinyl-1H-benzimidazole, mannitol and magnesium oxide were mixed with each other, hydroxypropylcellulose dissolved in ethanol was added to the mixture, the resultant mixture was granulated, dried and classified with a sieve of 28 mesh according to ASTM, the product being called (A). Then crystalline cellulose and corn starch were mixed with the product (A), hydroxypropylcellulose dissolved in water was added to the mixture, the resultant mixture was granulated, dried and classified with a sieve of 28 mesh, the product being called (B). The products (A) and (B), calcium salt of carboxymethylcellulose, talc and magnesium stearate were mixed with each other and the mixture was formed into plain tablets with a single shot tablet-formulating machine, being available from Okada Seiko-sha.

Ingredients of 1 plain tablet weighing 120.2 mg are shown below in units of mg:

20	2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]-methylsulfinyl-1H-benzimidazole	5.0
	mannitol	45.3
	magnesium oxide	40.0
	hydroxypropylcellulose	2.5
25	crystalline cellulose	10.0
	corn starch	10.0
	carboxymethylcellulose calcium	5.0
	talc	2.0
	magnesium stearate	0.2

30 The obtained plain tablets were coated with an enteric coating to obtain tablets.

Example 2

35 Tablets including 2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]-methylthio-1H-benzimidazole (I; n = 0) were prepared by the below shown prescription.

2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]-methylthio-1H-benzimidazole and mannitol were mixed with each other, hydroxypropylcellulose dissolved in ethanol was added to the mixture, the resultant mixture was granulated, dried and classified with a sieve of 28 mesh according to ASTM, the product being called (A). Then (A), crystalline cellulose, corn starch, calcium salt of carboxymethylcellulose, talc and magnesium stearate were mixed with each other and the mixture was formed into plain tablets with a single shot tablet-formulating machine, being available from Okada Seiko-sha.

Ingredients of 1 plain tablet weighing 99.7 mg are shown below in units of mg:

45	2-[4-(3-Methoxypropoxy)-3-methylpyridine-2-yl]-methylthio-1H-benzimidazole	5.0
	mannitol	65.3
	hydroxypropylcellulose	2.5
	crystalline cellulose	10.0
50	corn starch	10.0
	carboxymethylcellulose calcium	5.0
	talc	2.0
	magnesium stearate	0.2

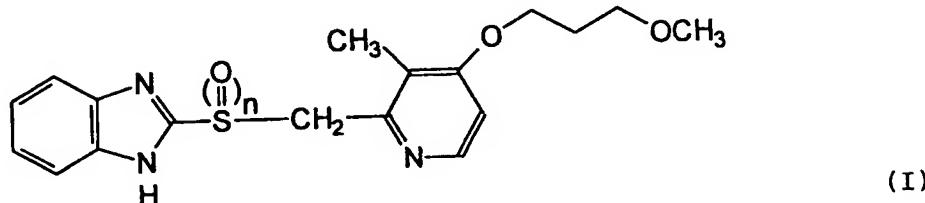
55 The obtained plain tablets were coated with an enteric coating to obtain tablets.

## Claims

1. The use of a pharmacologically effective amount of a compound having the following formula (I)

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wherein n is 0 or 1, or a pharmacologically acceptable salt thereof for the preparation of a medicament for preventing, improving or treating a disease caused by *Campylobacter pylori* in a mammal suffering from such a disease.

20 2. The use as claimed in Claim 1, wherein the mammal is a human being.

3. The use as claimed in Claim 1, wherein the disease is gastritis.

4. The use as claimed in Claim 3, in which the gastritis is recurrent.

25 5. The use as claimed in Claim 1, wherein the disease is diarrhea.

6. The use as claimed in Claim 1, wherein the disease is food poisoning.

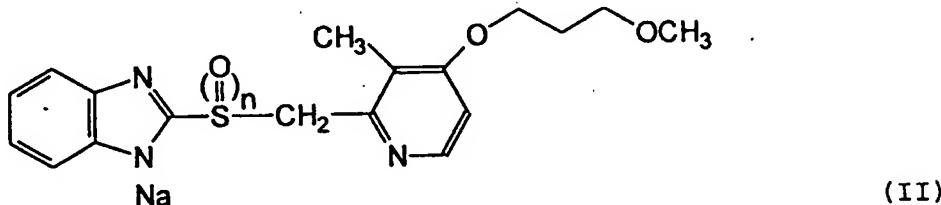
30 7. The use of a pharmacologically effective amount of a compound having the formula (I) as defined in claim 1 or a pharmacologically acceptable salt thereof for the preparation of a medicament for eradicating *Campylobacter pylori* from the mucous membrane of the stomach of a patient suffering from a gastric ulcer, duodenal ulcer or gastritis.

35 8. The use of a pharmacologically effective amount of a compound having the formula (I) as defined in claim 1 or a pharmacologically acceptable salt thereof for the preparation of a medicament for preventing recurrence of a disease caused by *Campylobacter pylori*.

40 9. The use of a pharmacologically effective amount of a compound having the formula (I) as defined in claim 1 or a pharmacologically acceptable salt thereof for the preparation of a medicament for restraining the adverse activity of *C. pylori* to cause a peptic disease.

45 10. The use according to any one of the preceding claims wherein the pharmaceutically active compound is employed as its sodium salt having the following formula (II):

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wherein n is 0 or 1.

**11. The use according to any one of the preceding claims, wherein the disease is peptic ulcer.**

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European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 93 11 3149

### DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL.S)
P,X	Dialog Information Services File 187, FDC Reports, 1987-93 Accession-no. 92407 The Pink Sheet vol. 55, issue 30, 26.7.93 'LYS-PRO modified insulin 1994 NDA filing a possibility, Lilly indicates; Lovan application has been switched to FDA Endocrine & Metabolism Division' *computer print-out*	1-11	A61K31/44
D,Y	EP-A-0 382 489 (TAKEDA CHEMICAL INDUSTRIES) * the whole document *	1-11	
Y	EUR. J. CLIN. MICROBIOL. INFECT. DIS. vol. 10, no. 2, 1991, pages 92 - 93 S. SUERBAUM ET AL. 'Antibacterial activity of pantoprazole and omeprazole against <i>Helicobacter pylori</i> ' * page 93, left column, last paragraph *	1-11	
D,A	EP-A-0 268 956 (EISAI CO. LTD.) * the whole document *	1-11	A61K TECHNICAL FIELDS SEARCHED (Int. CL.S)
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Eaminer	
MUNICH	26 NOVEMBER 1993	FOERSTER W.K.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			